Subpart C—Designation of an Orphan Drug

Subpart D—Orphan-Drug Exclusive Approval

Subpart E—Open Protocols for Investigations

Subpart F—Availability of Information

AUTHORITY: 21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371.

SOURCE: 57 FR 62085, Dec. 29, 1992, unless otherwise noted.

EDITORIAL NOTE: Nomenclature changes to part 316 appear at 69 FR 13717, Mar. 24, 2004.

Subpart A—General Provisions

§ 316.1 Scope of this part.

(a) This part implements sections 525, 526, 527, and 528 of the act and provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics. This part sets forth the procedures and requirements for:

(1) Submissions to FDA of:

(i) Requests for recommendations for investigations of drugs for rare diseases or conditions;

(ii) Requests for designation of a drug for a rare disease or condition; and

(iii) Requests for gaining exclusive approval for a drug for a rare disease or condition.

(2) Allowing a sponsor to provide an investigational drug under a treatment protocol to patients who need the drug for treatment of a rare disease or condition.

(b) This part does not apply to food, medical devices, or drugs for veterinary use.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[57 FR 62085, Dec. 29, 1992, as amended at 78 FR 35132, June 12, 2013]

§ 316.2 Purpose.

The purpose of this part is to establish standards and procedures for determining eligibility for the benefits provided for in section 2 of the Orphan Drug Act, including written recommendations for investigations of orphan drugs, a 7-year period of exclusive marketing, and treatment use of investigational orphan drugs. This part is also intended to satisfy Congress' requirements that FDA promulgate procedures for the implementation of sections 525(a) and 526(a) of the act.

§ 316.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act as amended by section 2 of the Orphan Drug Act (sections 525–528 (21 U.S.C. 360aa–360dd)).

(2) *Active moiety* means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative

(such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

(3) *Clinically superior* means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:

(i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or

(ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or

(iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

(4) *Director* means the Director of FDA's Office of Orphan Products Development.

(5) *FDA* means the Food and Drug Administration.

(6) *Holder* means the sponsor in whose name an orphan drug is designated and approved.

(7) *IND* means an investigational new drug application under part 312 of this chapter.

(8) *Manufacturer* means any person or agency engaged in the manufacture of a drug that is subject to investigation and approval under the act or the biologics provisions of the Public Health Service Act (42 U.S.C. 262–263).

(9) *Marketing application* means an application for approval of a new drug filed under section 505(b) of the act or an application for a biologics license submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

(10) *Orphan drug* means a drug intended for use in a rare disease or condition as defined in section 526 of the act.

(11) *Orphan-drug designation* means FDA's act of granting a request for designation under section 526 of the act.

(12) *Orphan-drug exclusive approval* or *exclusive approval* means that, effective on the date of FDA approval as stated in the approval letter of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years, except as otherwise provided by law or in this part. A designated drug will receive orphan-drug exclusive approval only if the same drug has not already been approved for the same use or indication.

(13) *Orphan subset of a non-rare disease or condition (''orphan subset'')* means that use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug.

(14) *Same drug* means:

(i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

(A) Two protein drugs would be considered the same if the only differences

in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences were shown to be clinically superior.

(B) Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were postpolymerization modifications, unless the subsequent drug could be shown to be clinically superior.

(C) Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, deoxyribose, or modifications of these sugars), unless the subsequent drug were shown to be clinically superior.

(D) Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior.

(15) *Sponsor* means the entity that assumes responsibility for a clinical or nonclinical investigation of a drug, including the responsibility for compliance with applicable provisions of the act and regulations. A sponsor may be an individual, partnership, corporation, or Government agency and may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of drugs. For purposes of the Orphan Drug Act, FDA considers the real party or parties in interest to be a sponsor.

[57 FR 62085, Dec. 29, 1992, as amended at 64 FR 402, Jan. 5, 1999; 64 FR 56449, Oct. 20, 1999; 78 FR 35132, June 12, 2013]

§ 316.4 Address for submissions.

All correspondence and requests for FDA action under the provisions of this rule should be addressed as follows: Office of Orphan Products Development, Food and Drug Administration, Bldg. 32, Rm. 5271, 10903 New Hampshire Ave., Silver Spring, MD 20993.

[78 FR 35133, June 12, 2013]

Subpart B—Written Recommendations for Investigations of Orphan Drugs

§ 316.10 Content and format of a request for written recommendations.

(a) A sponsor's request for written recommendations from FDA concerning the nonclinical and clinical investigations necessary for approval of a marketing application shall be submitted in the form and contain the information required in this section. FDA may require the sponsor to submit information in addition to that specified in paragraph (b) of this section if FDA determines that the sponsor's initial request does not contain adequate information on which to base recommendations.

(b) A sponsor shall submit two copies of a completed, dated, and signed request for written recommendations that contains the following:

(1) The sponsor's name and address.

(2) A statement that the sponsor is requesting written recommendations on orphan-drug development under section 525 of the act.

(3) The name of the sponsor's primary contact person and/or resident agent, and the person's title, address, and telephone number.

(4) The generic name and trade name, if any, of the drug and a list of the drug product's components or description of the drug product's formulation, and chemical and physical properties.

(5) The proposed dosage form and route of administration.

(6) A description of the disease or condition for which the drug is proposed to be investigated and the proposed indication or indications for use for such disease or condition.

(7) Current regulatory and marketing status and history of the drug product, including:

(i) Whether the product is the subject of an IND or a marketing application (if the product is the subject of an IND or a marketing application, the IND or